Attorney's Docket No. 1161 1027-014 (formerly BP94-03ACA4)
Expedited Procedure under 37 C F R 1 116
Examining Group 1653

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Maria S. Gawryl, Robert A. Houtchens and William R. Light

Application No.: 09/348,881 Group: 1653

Filed: July 7, 1999 Examiner: A. Gupta

For: PRESERVING A HEMOGLOBIN BLOOD SUBSTITUTE WITH A TRANSPARENT OVERWRAP

CERTIFICATE OF FACSIMILE TRANSMISSION
I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office
on 1/22/01 (Date) Carol M. Brown (Signature)
Carol M. Brown
Typed or printed name of person signing certificate

SUPPLEMENTAL DECLARATION OF ROBERT A. HOUTCHENS, PH.D. UNDER 37 C.F.R. § 1.132

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

I, Robert A. Houtchens, Ph.D., of 22 Briar Drive, Milford, Massachusetts 01757, declare as follows:

A. I received my Doctor of Philosophy degree from Colorado State University in 1980 in the field of biochemistry.

B. I am Associate Director, Process Development, of Research and Development at Biopure Corporation, Cambridge, Massachusetts, where I have been employed since 1990. My *curriculum vitae* is provided in Appendix I, attached.

C. My responsibilities include direction of research and process development, specifically with regard to scale-up of centrifugation, ultrafiltration,

microfiltration and chromatographic separation processes associated with preparation of hemoglobin solutions. I also am responsible for optimization of current manufacturing processes, research into new manufacturing technologies, and scale-up and manufacture of chromatographic media associated with preparation of hemoglobin solutions, and packaging of deoxygenated hemoglobin solutions.

D. I have read U.S. patent application 09/348,881. I understand the application, the pending Office Action, dated November 7, 2000, and the issues relating to patentability presented by the Examiner in the Office Action for the invention claimed in the patent application.

E. I have read and I understand U.S. 5,234,903, issued to Nho, *et al.*, U.S. 4,561,110, issued to Herbert, U.S. 4,826,955, issued to Akkapeddi, *et al.*, U.S. 4,699,816, issued to Galli, and Dodrill, *et al.*, "Barrier Coated Polyester Film for Healthcare Packaging," *Conference Paper presented at the "Polyester in Healthcare Packaging."* pp. 1-17, all of which were cited by the Examiner in the Office Action dated February 18, 2000.

F. In reply to the Office Action, I hereby state the following as my opinion, as one who is of at least ordinary skill in the art of packaging deoxygenated hemoglobin blood substitutes:

1. Because of a relatively high affinity of deoxygenated hemoglobin for oxygen, containment of the deoxygenated hemoglobin within a transparent overwrap that includes an ethylene vinyl alcohol layer as an oxygen barrier would cause the oxygen gradient across the transparent laminate overwrap to be maintained at a high level over an extended period of time, relative to other liquids, such as water, that do not exhibit the same affinity for oxygen.
2. Because of a relatively high affinity of deoxygenated hemoglobin for ~~water~~, the volume of oxygen that would permeate a transparent laminate

oxygen RH
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material employed as an overwrap for deoxygenated hemoglobin would be expected by one of ordinary skill in the art to be significantly greater than the amount of oxygen that would be expected to be transported across the same laminate when employed as an overwrap for a liquid, such as water, that did not exhibit the same affinity for oxygen as deoxygenated hemoglobin.

3 The demonstrated ability of the claimed method to preserve a deoxygenated hemoglobin blood substitute would not be expected by one of ordinary skill in the art from the observed oxygen permeability of ethylene vinyl alcohol because, *inter alia*, deoxygenated hemoglobin has an affinity for oxygen that would maintain an oxygen gradient across the laminate over an extended period of time that is relatively high, as compared to other liquids, such as water, that do not exhibit the same affinity for oxygen.

4. Further to the statements made in my Declaration of August 17, 2000, it is my opinion that one of ordinary skill in the art would not expect to see the amounts of methemoglobin measured in the deoxygenated hemoglobin blood substitute stored in the manner described in Example 4 of the instant specification because of a relatively high affinity of deoxygenated hemoglobin for oxygen.

5. Despite the known oxygen permeability of ethylene vinyl alcohol, one of ordinary skill in the art would not expect to be able to maintain substantially the deoxygenated state of a hemoglobin blood substitute by containing the deoxygenated hemoglobin blood substitute within an oxygen barrier film overwrap, wherein the oxygen barrier film overwrap includes a transparent laminate material that includes an ethylene vinyl alcohol layer and has an oxygen permeability of less than about 0.01 cubic centimeters per 100 square inches over 24 hours at 1 atmosphere and at room temperature.

6. One of ordinary skill in the art would not expect, in view of Nho, *et al.*, Dodrill or Hong, *et al.*, taken either separately or in combination, to be able to preserve deoxygenated hemoglobin within an oxygen barrier film overwrap that includes a transparent laminate material having an ethylene vinyl alcohol layer, and wherein the oxygen permeability of the laminate material is less than about 0.01 cubic centimeters per 100 square inches over 24 hours at 1 atmosphere, at room temperature, and at 0% relative humidity.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements, if made, may jeopardize the validity of the application or any patent issuing thereon.

Robert A. Houtchens

Robert A. Houtchens, Ph.D.

22 JAN 01

Date

APPENDIX I

Robert A. Houtchens, Ph.D.

CURRICULUM VITAE

Name: Robert A. Houtchens, Ph.D.

Date and Place of Birth: March 31, 1953, Denver, Colorado

Education:

1980 Ph.D. - Colorado State University, Biochemistry

1975 B.S. - Colorado State University, Biochemical Engineering

Brief Chronology of Employment:

1997-2000 Associate Director, Process Development
Research and Development
Biopure Corporation, Cambridge, MA

Responsibilities: Direction of research in process development. Scale-up of centrifugation, ultrafiltration, microfiltration and chromatographic separation processes. Optimization of current manufacturing processes. Research into new manufacturing technologies. Scale-up and manufacture of chromatographic media. Validation of process inactivation/removal of potential viruses, TSE's.

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Responsibilities: Management of research in process development and bioanalytical chemistry.

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Responsibilities: Research in process development and bioanalytical chemistry.

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Dow Chemical Company, Midland, MI

Responsibilities: Research in the area of protein insect toxins. Construction of hybrid insect toxins, isolation of high purity insect toxins from venoms and direction of synthesis of peptides models. Bioanalytical characterization of protein insect toxins.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Application No.:	09/348,881	Group:	1653
Filed:	July 7, 1999	Examiner:	A. Gupta
For:	PRESERVING A HEMOGLOBIN BLOOD SUBSTITUTE WITH A TRANSPARENT OVERWRAP		

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231

on 8/18/00 Carol M. Brown
Date Signature

Carol M. Brown
Typed or printed name of person signing certificate

DECLARATION OF ROBERT A. HOUTCHENS, PH.D. UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

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F. In reply to the Office Action, I hereby state the following as my opinion, as one who is of at least ordinary skill in the art of packaging deoxygenated hemoglobin blood substitutes:

1. Example 4 of the specification in the instant patent application is one embodiment of the claimed invention, wherein deoxygenated hemoglobin was stored in a primary package of polyethylene (2 mil) and nylon (2 mil). The primary package was overwrapped in a transparent laminate overwrap that included a layer of ethylene vinyl alcohol copolymer (ethylene vinyl alcohol) sealed between two layers of polypropylene. As described in Example 4, the deoxygenated hemoglobin blood substitute, packaged within the primary package and the transparent laminate overwrap, was stored at about 40°C in an atmosphere of about 60% relative humidity (RH) for a period of about twelve months. The concentrations of various

components were measured initially, and at three-month intervals through the twelve-month period. The results are shown in Table 4 at page 35 of the specification.

2. One of ordinary skill in the art would not expect to see the amounts of methemoglobin measured in the deoxygenated hemoglobin blood substitute stored in the manner described in Example 4. More specifically, one of ordinary skill in the art would not expect that the deoxygenated hemoglobin blood substitute stored in the primary package and overwrapped with a transparent laminate package as described in Example 4, and under the conditions set forth in Example 4, to have the methemoglobin content that was measured.

3. One of ordinary skill in the art would expect that, without the presence of the overwrap, the methemoglobin content of the deoxygenated hemoglobin blood substitute would approximate 100% of the hemoglobin content available at the conclusion of the twelve-month period of testing.

4. One of ordinary skill in the art would not expect that an oxygen barrier film laminate that includes an ethylene vinyl alcohol layer, as employed in the overwrap layer of Example 4, would limit the percent methemoglobin to the level observed following storage over a period of twelve months under the conditions described.

5. Neither Nho, *et al.* nor Herbert, taken either separately or in combination, would motivate one ordinary skill in the art to employ an overwrap employing an ethylene vinyl alcohol layer to package a deoxygenated hemoglobin blood substitute contained within a primary package.

6. The permeability to oxygen observed under the conditions described in Example 4, as evidenced by the percent methemoglobin found in the hemoglobin solution after twelve months of storage under the conditions

set forth, would be unexpected to one of ordinary skill in the art of blood or blood substitute packaging.

7. Dodrill, *et al.* do not disclose or suggest employment of ethylene vinyl alcohol as a layer in an oxygen barrier film overwrap for deoxygenated hemoglobin in a primary package. Further, neither Dodrill, *et al.* nor Nho, *et al.*, taken either separately or in combination, suggest the claimed invention of the instant application.

8. Applicants' claimed invention has demonstrated an unexpected ability to limit methemoglobin content of the oxygenated hemoglobin blood solution over a period of twelve months at 40°C and 60% relative humidity in the surrounding atmosphere. This result would be unexpected to one of ordinary skill in the art in view of the teachings of Dodrill, *et al.* and Nho, *et al.*, taken separately or in combination.

9. One of ordinary skill in the art would not expect, based on the teachings of Galli or Akkapeddi, *et al.*, taken either separately or in combination with each other, or in combination with either or both of Nho, *et al.* and Dodrill, *et al.*, to obtain the result observed by employing an oxygen barrier film overwrap that includes an ethylene vinyl alcohol layer to preserve a deoxygenated hemoglobin blood substitute contained within a primary package, as shown in Example 4 of the instant application.

10. Based on the teachings of Galli, Akkapeddi *et al.*, Nho, *et al.* and Dodrill, *et al.*, one of ordinary skill in the art would expect that the relative humidity employed in Example 4 would cause the methemoglobin content of the deoxygenated hemoglobin blood substitute to be much higher than the 7.9% value measured.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements, if made, may jeopardize the validity of the application or any patent issuing thereon.

Robert A. Houtchens

Robert A. Houtchens, Ph.D.

17 AUG 00

Date

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Responsibilities: Research in the area of protein insect toxins. Construction of hybrid insect toxins, isolation of high purity insect toxins from venoms and direction of synthesis of peptides models. Bioanalytical characterization of protein insect toxins.

DOCKET NO. 1161.1027-064

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

In re Application of:	Maria S. Gawryl, Robert A. Houtchens and William R. Light
Application No.:	10/018,399
Filed (371(c)):	May 22, 2002
Confirmation No.:	8372
For:	PRESERVING A HEMOGLOBIN BLOOD SUBSTITUTE WITH A TRANSPARENT OVERWRAP

The owner, Biopure Corporation of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent Nos. 6,288,027 and 6,271,351. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The terminal disclaimer fee under 37 CFR 1.20(d) is enclosed.

The undersigned is empowered to act on behalf of the owner.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1 April 05
Date

Signature

Carl W. Rausch
Typed or printed name

Biopure Corporation

Docket No. 1161.1027-064

STATEMENT UNDER 37 C.F.R. § 3.73(b)

Inventor(s): Maria S. Gawryl, Robert A. Houtchens and William R. Light

Application No./Patent No.: 10/018,599 Filed (371(c)): May 22, 2002

For: PRESERVING A HEMOGLOBIN BLOOD SUBSTITUTE WITH A TRANSPARENT OVERWRAP

Biopure Corporation (Name of Assignee), a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is

A. [X] the assignee of the entire right, title and interest in the patent application identified above; or

B. [ ] an assignee together with [ ] of the entire right, title and interest in the patent application identified above.

The right, title and interest of the above-named assignee in the patent application identified above is established by virtue of:

A. [X] An assignment from the inventor(s) of the patent application identified above. The assignment was recorded in the Patent and Trademark Office at Reel 012929, Frame 0553-0556, or a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s) of the patent application identified above, to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature: Carl W. Rausch

Name: Carl W. Rausch

Title: Cofounder and Vice Chairman and Chief Technology Officer

Date: April 05